

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING
TRANSMITTAL OF COPY OF INTERNATIONAL
PRELIMINARY REPORT ON PATENTABILITY
(CHAPTER I OF THE PATENT COOPERATION
TREATY)
(PCT Rule 44bis.1(c))

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| Date of mailing (<i>day/month/year</i>) 29 June 2006 (29.06.2006) |
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To:

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| |
|---|
| Applicant's or agent's file reference 04578J49 |
|---|

IMPORTANT NOTICE

| | | |
|--|--|--|
| International application No. PCT/IB2004/004128 | International filing date (<i>day/month/year</i>) 15 December 2004 (15.12.2004) | Priority date (<i>day/month/year</i>) 17 December 2003 (17.12.2003) |
| Applicant GLYCORES 2000 S.R.L. et al | | |

The International Bureau transmits herewith a copy of the international preliminary report on patentability (Chapter I of the Patent Cooperation Treaty)

The International Bureau of WIPO
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

| | | | |
|--|--|--|------------------|
| Applicant's or agent's file reference 04578J49 | FOR FURTHER ACTION | | See item 4 below |
| International application No. PCT/IB2004/004128 | International filing date (<i>day/month/year</i>) 15 December 2004 (15.12.2004) | Priority date (<i>day/month/year</i>) 17 December 2003 (17.12.2003) | |
| International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237 | | | |
| Applicant GLYCORES 2000 S.R.L. | | | |

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).
2. This REPORT consists of a total of 9 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

- | | | |
|-------------------------------------|--------------|---|
| <input checked="" type="checkbox"/> | Box No. I | Basis of the report |
| <input type="checkbox"/> | Box No. II | Priority |
| <input type="checkbox"/> | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| <input type="checkbox"/> | Box No. IV | Lack of unity of invention |
| <input checked="" type="checkbox"/> | Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input checked="" type="checkbox"/> | Box No. VI | Certain documents cited |
| <input checked="" type="checkbox"/> | Box No. VII | Certain defects in the international application |
| <input checked="" type="checkbox"/> | Box No. VIII | Certain observations on the international application |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

Date of issuance of this report
20 June 2006 (20.06.2006)

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|---|---|
| The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 740 14 35 | Authorized officer Cecile Chatel Telephone No. +41 22 338 70 60 |
|---|---|

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

REC'D 22 JUN 2005
WIPO PCT

PCT

To:

see form PCT/ISA/220

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

FOR FURTHER ACTION

See paragraph 2 below

Applicant's or agent's file reference
see form PCT/ISA/220

International application No.
PCT/IB2004/004128

International filing date (day/month/year)
15.12.2004

Priority date (day/month/year)
17.12.2003

International Patent Classification (IPC) or both national classification and IPC
C08B37/10, C08B37/00, A61K31/726, A61K31/727, A61K31/737

Applicant
GLYCORES 2000 S.R.L.

1. This opinion contains indications relating to the following items:

- Box No. I Basis of the opinion
- Box No. II Priority
- Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- Box No. IV Lack of unity of invention
- Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- Box No. VI Certain documents cited
- Box No. VII Certain defects in the international application
- Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IB2004/004128

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 a sequence listing
 table(s) related to the sequence listing
 - b. format of material:
 in written format
 in computer readable form
 - c. time of filing/furnishing:
 contained in the international application as filed.
 filed together with the international application in computer readable form.
 furnished subsequently to this Authority for the purposes of search.
3. In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IB2004/004128

**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or
industrial applicability; citations and explanations supporting such statement**

1. Statement

| | | |
|---------------------|------|---------------------------------|
| Novelty (N) | Yes: | Claims 4-16,20,22,26 |
| | No: | Claims 1-3,17-19,21,23-25,27-35 |
| Inventive step (IS) | Yes: | Claims 4-16,20,22,26 |
| | No: | Claims |

Industrial applicability (IA) Yes: Claims 1-27,32-35
No: Claims

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43bis.1 and 70.10)

and /or

2. Non-written disclosures (Rules 43bis.1 and 70.9)

see form 210

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

**Reasoned statement with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1. Cited literature

- (a) Reference is made to the following documents:

D1: US-A-2002 0 062 019
D2: WO-A-02 50 125
D3: US-A-5 314 876
D4: WO-A-97 43 317
D5: WO-A-02 068 477

- (b) In the following arguments, page or column A, lines B to C will be cited as A/B-C.

2. Preliminary remarks

Ranges blurred by the word "about" or similar terms "... prevent the invention from being unambiguously distinguished from the prior art, ..." (PCT Examination Guidelines 5.38).

Therefore, such ranges in claims 5-8, 14, 15, 18, 19, 21-23, 34 and 35 were not taken into account when assessing novelty and inventive step.

3. Novelty

- (a) Document D1 teaches in claim 64 a method for controlling coagulation in a mammal by administering an epimerised K5-N,O-sulfate having a sulfation degree of from 2.3 to 9 and wherein 40-60% of the uronic acid units are iduronic acid units. The subject-matter of the following claims is not novel in view of the following disclosure in D1:
claims 1, 17,

- 27-29: D1, claims 17 and 35;
claim 2: D1, claims 32, 33;
claim 3: D1, claim 34;
claim 18-21: D1, examples 7-b, 10-B and 11 (see Table 2 on page 14);
claim 23: D1, claim 38;
claims 30, 31: D1, claims 67-70.

(b) Document **D2** discloses in example 2 a depolymerised, C5-epimerised K5-N,O-sulfate wherein

- (a) 54% of the glucuronic acid units are iduronic acid units,
- (b) the degree of sulfation is 2.55 and the
- (c) average molecular weight is 7 400.

It is produced by K5 (i) N-deacetylation, (ii) N-sulfation, (iii) epimerisation, (iv) formation of the tetrabutylammonium salt and oversulfation, (v) selective O-desulfation, (vi) O-sulfation, (vii) N-sulfation and (viii) depolymerisation with nitrous acid (see also claims 22, 25 and 39-41).

Document **D3** reports on 14/25-64 that depolymerisation with nitrous acid leads to terminal 2,5-anhydromannitol units.

Therefore, the subject-matter of claims 17-19, 21, 23-25 and 27-31 is not novel in view of **D2**.

(c) Document **D4** discloses in examples 2 and 3 K5 polysaccharides

- which are 60% or 55% epimerised,
- have a mean molecular weight of 14,000,
- a degree of sulfation of 2.3 and 2.4, resp.,
- and which are 6-O-sulfated to 90 or 70 %, resp..

So, the subject-matter of claims 17, 23 and 27-31 (see claim 12) is also not novel in view of **D4**.

(d) Document **D5** discloses in claims 20, 23 and 32 a pharmaceutical composition containing

- (a) an N,O-oversulfated K5 having a sulfation degree of from 3.5 to 4 and a mean molecular weight of about 6,500, and
- (b) a pharmaceutical excipient or vehicle.

In examples 2 and 3 sulfation degrees of 3.84 and 3.54 are reported and the polysaccharides are obtained as sodium salts (see 15/21-22). The product of example 3 has a mean molecular weight of 13,000.

The subject-matter of claims 32-35 thus is not novel.

3. Inventive step

- (a) The document **D2** is regarded as being the closest prior art to the subject-matter of process claims 1 to 16.
- (b) The process of **D2** differs from the one of present claims 1 to 16 in that **D2** teaches depolymerisation as a final step whereas the present claims require a depolymerised K5 polysaccharide as the starting material.
- (c) It is not evident which technical problem is solved by this differing sequence in the process steps known from **D2** other than to provide an alternative process.
- (d) It is evident, e.g. from **D5** (see **D5**, 9/7-15) that the depolymerisation with nitrous acid may also be conducted at an earlier stage, i.e. before O-sulfation. Therefore, the subject-matter of claims 4-16 is not based on an inventive step.
- (e) Dependent claims 20, 22 and 26 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step.

4. Industrial applicability

Claims 28 to 31 relate to subject-matter considered by this Authority to be covered

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/IB2004/004128

by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

**Re Item VI
Certain documents cited**

Certain published documents

| Application No Patent No | Publication date (day/month/year) | Filing date (day/month/year) | Priority date (valid claim) (day/month/year) |
|--------------------------------|--------------------------------------|--|---|
| WO-A-03 106 504 | 24.12.2003 | 17.06.2003 | |
| Kind of non-written disclosure | | Date of non-written disclosure (day/month/year) | Date of written disclosure referring to non-written disclosure (day/month/year) |

This document discloses in claim 48 a low molecular weight epi-K5-amine-O-versulfate in which

- 40% to 60 % of the uronic acid units are iduronic acid units
- the sulfation degree is at least 3.4, and
- which has a sulfated 2,5-anhydromannitol as the terminal unit at the reductive end.

In example 4 (b) the epi-K5-amine-O-versulfate has a sulfation degree of 3.55. These polysaccharides are to be admixed to excipients to form pharmaceutical compositions (see 36/4-18).

It thus discloses the subject-matter of claims 32-35.

**Re Item VII
Certain defects in the international application**

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/IB2004/004128

- 1- In claim 23 at 39/25, the expression "anidromannitol" should be replaced by "anhydromannitol"
- 2- The expression "incorporated herein by reference" or the like at 7/4-5 and 7/16 leaves doubt as to the actual disclosure of the present application and should be deleted.

Re Item VIII

Certain observations on the international application

Clarity of the claims

The word "about" blurs the ranges given in claims 5-8, 14, 15, 18, 19, 21-23, 34 and 35 thus rendering these claims unclear.